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WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
GANGLE, BRIAN J	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
tina.dougal@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	09/890,335	CEVC ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-79* is/are pending in the application.

4a) Of the above claim(s) *46,49,51-54,56,57,61 and 68-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-45,47,48,50,55,58-60 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/2006*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 20070628
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment, filed 4/16/2007, and remarks, filed 10/27/2006, are acknowledged. Claims 37-79 are pending. Claims and 37-38, 40, 42, 48, 58-59 are amended. Claims 46, 49, 51-54, 56-57, 61, and 68-79 are withdrawn as being drawn to non-elected inventions. Claims 37-45, 47-48, 50, 55, 58-60, and 62-67 are currently under examination.

Information Disclosure Statement

The information disclosure statement, filed 10/27/2006, has been considered. An initialed copy is enclosed. References BA-BC have not been considered because no English language translation was available. These references will be considered as translations become available.

Claim Objections Withdrawn

The objection to claims 37-45, 47-48, 50, 55, 58-60, and 62-67 because the claims are drawn, in part, to non-elected inventions, is withdrawn. Applicant is correct regarding the appropriateness of non-elected species in claims.

The objection to claim 58 because the claims recites the phrase "wherein the low molecular weight irritant from the group of surfactant-like molecules," is withdrawn in light of applicant's amendment.

Claim Rejections Withdrawn

The rejection of claim 37 as being rendered vague and indefinite by the phrase "an antigen or mixture thereof," is withdrawn in light of applicant's amendment.

The rejection of claim 38 as being rendered vague and indefinite by the phrase "wherein the at least two substances are two different forms of a substance," is withdrawn in light of applicant's amendment.

The rejection of claims 40, 58-59 as being rendered vague and indefinite by the phrase "surfactant-like molecule," is withdrawn in light of applicant's amendment.

The rejection of claim 42 as being rendered vague and indefinite by the phrase "wherein the total weight of droplets in the vaccine for use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total mass," is withdrawn in light of applicant's amendment.

The rejection of claim 48 as being rendered vague and indefinite by the phrase "pathogens triggering tetanus," is withdrawn in light of applicant's amendment.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 37-45, 47-48, 50, 55, 58-60, and 62-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That the specification provides sufficient distinguishing characteristics for vaccine compositions comprising antigens or allergens other than tetanus toxoid. As an example, applicant points to where the specification lists a group of pathogens from which the antigen can be derived. Applicant argues that because the specification lists these pathogens, as well as compounds from pathogens that can serve as antigens (e.g. lipids, carbohydrates, and proteins),

the specification provides "more than adequate written description for vaccines comprising antigens other than tetanus toxoid."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, merely listing pathogens and mentioning virtually every class of molecule that can be found in them does not show that applicant was in possession of all of these molecules, nor does it provide support for vaccines against these pathogens. In fact, it is quite clear that applicant does not have possession of the scope of the claimed invention. This is evidenced by the list of pathogens found in the specification. The list includes HIV and rhinovirus. To date, no vaccines against either of these pathogens is available. Moreover, as applicant extensively argued in their remarks filed 3/14/2006 (in the response to the restriction requirement), a composition that comprises an antigen (even if it induces an antibody response) is not the same as a vaccine. A vaccine requires the induction of protective immunity. It is well known in the art that this can only be demonstrated by pathogen challenge experiments in a reasonable model system. Applicant has shown no evidence whatsoever that any antigen other than tetanus toxoid is capable of inducing protective immunity when delivered by the claimed transdermal composition. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

As outlined previously, the instant claims are drawn to a transdermal vaccine that comprises a transdermal carrier, a compound which specifically has or induces cytokine or anti-cytokine activity, and an antigen derived from pathogens triggering tetanus. The claims encompass all antigens that can be derived from pathogens triggering tetanus, including proteins, cell wall constituents, and the tetanus toxin of *Clostridium tetani*. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from

others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of antigens derived from pathogens triggering tetanus, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit a protective immune response when administered transdermally.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of antigens to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (to elicit a protective immune response against pathogens triggering tetanus), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of antigens. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of antigens that can be derived from pathogens triggering tetanus.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical*

Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore,

absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antigens that can be derived from pathogens triggering tetanus. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of antigens to which the claims refer. Hence, only a vaccine containing tetanus toxoid meets the written description requirements.

The rejection of claims 37-45, 47-48, 50, 55, 58-60, and 62-67 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising tetanus toxoid as the antigen, does not reasonably provide enablement for vaccines comprising an antigen derived from pathogens triggering tetanus, is maintained for the reasons set forth in the previous office action.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. That the specification enables the making and use of vaccine compositions because the experiments for determining whether an antigen produces protective immunity require only routine experimentation. Applicant points to the examples in the specification where tetanus toxoid is used as a vaccine. Applicant asserts that the specification provides sufficient disclosure of pathogens and the range of compounds derived from such pathogens that can be used to generate an immune response.

2. That "those of skill in the art recognize that new technologies have allowed vaccine researchers to produce proteins quickly for vaccine testing."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the experiments for determining whether an antigen induces protective immunity are not routine. They require the use of techniques that are well known, but the process itself is not routine. Each candidate antigen must be isolated, identified, produced in various forms, then tested in animal models which often require a great deal of work to develop.

Moreover, there are many diseases (e.g. gonorrhea) that lack animal models. Additionaly, the instant claims encompass an incalculable number of molecules, many of which have not been described or isolated. It is well known to those skilled in the vaccine art, that making a vaccine is not simply a matter of picking an antigen. If it were simply a matter of picking an antigen, there would already be vaccines for every disease known to man. Further, merely listing a pathogen in the specification does not provide support for a vaccine against that pathogen. For example, the specification lists HIV and rhinovirus as pathogens the instant vaccine can be used against. However, to date, there is no vaccine against HIV or rhinovirus.

Regarding argument 2, applicant is correct in their assertion that those of skill in the art recognize that new technologies have allowed vaccine researchers to produce proteins quickly for vaccine testing. However, it is noted that these technologies allow vaccine researchers to produce proteins quickly for vaccine *testing*. This does not mean that the development of a vaccine is routine. In fact, a reading of the entire reference applicant refers to (Ellis), shows that vaccine development is a difficult process. Ellis points out that there are multiple strategies for the development of vaccines (something which would not be needed it vaccines were simply a matter of picking an antigen) and on page 571, column 2, states, "because of the biology of the disease or the nature of the immune response induced by the vaccine, it is important to realize that recombinant vaccines do not always provide the solution to the problem of prevention of an infectious disease."

As outlined previously:

Nature of the invention: The instant claims are drawn to a transdermal vaccine that comprises a transdermal carrier, a compound which specifically has or induces cytokine or anti-cytokine activity, and an antigen derived from pathogens triggering tetanus. The claim encompasses all antigens that can be found in, and are expressed by, a *Clostridium tetani* cell, including proteins, cell wall constituents, and the tetanus toxin.

Guidance of the specification/The existence of working examples: The specification discloses, in the examples, challenge experiments using the claimed vaccine wherein the antigen is tetanus toxoid. The specification is devoid of any teaching that any antigen other than the tetanus toxoid provides an effective vaccine against any disease, when administered transdermally. To be a prophylactic composition, the composition must elicit protective

immunity, demonstrable by pathogen challenge experiments in a reasonable model system. The skilled artisan would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon the transdermal administration in any animal model of disease by all of the antigens encompassed by the claims. Therefore it is not clear which of the claimed antigens are capable of generating a protective immune response against a given disease, when administered transdermally.

State of the art: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar *et al.*, US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, *et al.* (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies... and thus protect the host against attack by the pathogen."

The specification fails to teach that any of the claimed antigens other than the tetanus toxoid can produce a protective response in the host, as is requisite of a vaccine composition. In view of the lack of support in the art and specification for an effective vaccine comprising the claimed proteins, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the full scope of the claims are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 37 as being rendered vague and indefinite by the phrase "the penetrant in the form of a minute fluid droplet surrounded by a coating of one or more layers of

at least 2 substances that differ by at least a factor of 10 in solubility in a liquid medium," is maintained for the following reasons set forth in the previous office action.

Regarding the portion of the rejection stating that it is unclear how one can have one layer of 2 substances:

Applicant argues: that a layer can be composed of one or more substances. Applicant asserts that the specification discloses vesicles having a coating comprising a first substance that is more soluble and a second substance that is less soluble, and that this coating is a single layer.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's assertion that a coating comprising a first substance that is more soluble and a second substance that is less soluble is incorrect. If the solubility of these substances differs by at least a factor of 10, as is required by the claims, the two substances would not form a single layer.

Regarding the portion of the rejection stating that if the antigen or allergen is not actually found in the penetrant, it would not penetrate the skin, and would therefore be unable to cause an immune response:

Applicant argues: that one of skill in the art would understand that the antigen or allergen is mixed with the penetrant to allow for movement across a barrier.

Applicant's arguments have been fully considered and deemed non-persuasive.

According to applicant's arguments and the specification, the penetrant is the droplet surrounded by a coating. It is the structure of these droplets that allows them to deform and penetrate the skin. The claim is drawn to a composition that has these droplets as well as an antigen. Applicant asserts that merely mixing the antigen with these penetrant droplets would allow for movement across a barrier. This is not the case. The specification and the art do not support such an assertion. The examples in the specification do not show antigen merely mixed with penetrant droplets, but rather show that the antigen is mixed with the solution used to form the droplets, *before* the droplets are actually formed. It is clear from both the specification and the art that the antigen must be in the droplet to cross the barrier of the skin.

The rejection of claim 39 as being rendered vague and indefinite by the phrase "the antigen or allergen are associated with the penetrant," is maintained for the reasons set forth in the previous office action.

Applicant argues: that the term "association" is used within the field of chemistry to mean a "combination, connection, or correlation of substances." Applicant asserts that "associated" is meant to encompass "combined or connected physically with the penetrant," rather than being free in the penetrant composition, and that one of skill in the art would understand what the distinction of claim 39 is over claim 37.

Applicant's arguments have been fully considered and deemed non-persuasive.

Merely stating that "one of skill in the art would understand" does not explain away the deficiencies of the claim raised by the examiner. It is quite clear what the definition of the term "associated" is. It is the use of the term in the context of claims 37 and 39 that renders the rejected claim unclear. It is not clear is how claim 39 is different from claim 37. As applicant argues, the term "association" is used within the field of chemistry to mean a "combination, connection, or correlation of substances." Therefore, in claim 37, the antigen is "associated" with the penetrant. Applicant states that "associated" is meant to encompass "combined or connected physically with the penetrant," rather than being free in the penetrant composition. The problem with this statement is that applicant does not define the word associated, but states what it encompasses. This means that the term also encompasses other meanings, and those of skill in the art have no way of knowing which "definition" applicant has chosen to apply to claim 39 and which definition is to apply to claim 37. Moreover, the definition presented by applicant (from Grant and Hackh's Chemical Dictionary, a copy of which applicant has neglected to make of record) applies to both claim 37 and claim 39. Applicant is reminded that, according to MPEP 2111.01, "Although claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004) (The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation in light of the specification.). This means that the

words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (discussed below); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004) (Ordinary, simple English words whose meaning is clear and unquestionable, absent any indication that their use in a particular context changes their meaning, are construed to mean exactly what they say. Thus, "heating the resulting batter-coated dough to a temperature in the range of about 400°F to 850°F" required heating the dough, rather than the air inside an oven, to the specified temperature.)."

As outlined previously, it is not clear what the term "associated" is intended to mean. According to the parent claim, the antigen or allergen and penetrant are already in a vaccine composition, and are thus associated. Does applicant intend that there be some other form of association?

The rejection of claim 47 as being rendered vague and indefinite by the phrase "derived from," is maintained for the reasons set forth in the previous office action.

Applicant argues: that the term has an ordinary meaning well known to those of skill in the art. Applicant argues that the term means "to receive or obtain from a source," and that in the context of claim 47, this means that the antigen is obtained from a pathogen.

Applicant's arguments have been fully considered and deemed non-persuasive.

The examiner understands that the term "derived from" is equivalent to "obtained from." However, the definition of "derived" includes things that are only originally or theoretically obtained from a particular source. Therefore the term implies that the antigen has undergone some sort of change. It is not clear what degree of change is acceptable or what properties of the antigen must be maintained when someone is "deriving" the antigen. Further, various microorganisms (including pathogens) can be used to recombinantly produce antigenic molecules. If someone used *E. coli* to recombinantly produce bovine albumin, the albumin would be an antigen derived from a pathogen, but it would not be capable of inducing a protective immune response against that pathogen.

As outlined previously, it is unclear what the term "derived from" is intended to mean.

The rejection of claim 50 as being rendered vague and indefinite by the phrase "wherein the concentration of each compound used," is maintained for the reasons set forth in the previous office action.

Applicant argues: that the term "compound" is recited in parent claim 37 and is used to describe those compounds that have or induce cytokine or anti-cytokine activity. Applicant asserts that it is not used to describe any other vaccine component.

Applicant's arguments have been fully considered and deemed non-persuasive.

One only combines the word "each" with the word "compound" if there is more than one compound being referred to. If there is only a single compound being described, it is not grammatically correct to refer to multiple compounds; one would simply refer to "the compound" or "said compound." Therefore, in claim 50, applicant is clearly referring to multiple compounds from claim 37. Since the vaccine composition of claim 37 only contains *a* compound which specifically has or induces cytokine or anti-cytokine activity (the word *a* clearly implies that there is only one), the phrase "each compound" in claim 50 must be referring to compounds in addition to the "compound which specifically has or induces cytokine or anti-cytokine activity." As each of the components of the vaccine in claim 37 is a compound (by definition), it is not clear which compounds applicant intends the claim to refer to.

As outlined previously, to what compounds is applicant referring? Does applicant mean the compound which specifically has or induces cytokine or anti-cytokine activity, or does applicant mean each of the compounds used to make up the vaccine?

The rejection of claims 44, 58, and 69 based on the use of the term "low molecular weight irritant," is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That those of skill in the art use the term "low molecular weight" to refer to molecules that are of lower molecular weight than other molecules within a particular class. Applicant asserts that the term "low molecular weight irritants" includes molecules of low molecular weight as compared to large protein irritants.

2. That the specification describes a "low molecular weight irritant" as classes of allergenic metal ions, acids, bases, irritating fluids, etc.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, stating that "low" means lower than other things in the same class does not define the limits of what is encompassed by the word "low." For example, nitric acid has a lower molecular weight than sulfuric acid; therefore, nitric acid should be considered to be a "low molecular weight" compound. However, nitric acid has a higher molecular weight than hydrochloric acid; therefore, nitric acid cannot be considered to be a "low molecular weight" compound.

Regarding argument 2, the specification does not define the term "low molecular weight irritant." The pages to which applicant refers merely state that, in a preferred embodiment, the "low molecular weight irritant" is selected from various classes of molecule. This does not define the limits of what is encompassed by the word "low."

As outlined previously, in claims 44, 58, and 60 the term "low molecular weight irritant," is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The rejection of claim 65 as being rendered vague and indefinite by the phrase "pure or purified antigen," is maintained for the reasons set forth in the previous office action.

Applicant argues: that the term "pure" means "unadulterated, free from admixture or contamination with extraneous matter." Applicant also argues that the term "purified" means "to remove unwanted constituents from a substance." In addition, applicant states, "pure antigen can be obtained from common commercial sources, which provide the degree of purity." It is applicant's assertion that one of skill in the art would readily understand what the terms "pure" and "purified" mean and to what degree of purity the claim is referring.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's arguments demonstrate the validity of the rejection. Applicant has provided two definitions that do not agree. "Pure" antigen according to the first definition must be "unadulterated, free from admixture or contamination with extraneous matter." "Pure" antigen according to the second definition must merely have had unwanted constituents removed. This is not the same as having had all unwanted constituents removed. For example, if DNA is to

serve as the antigen, one could lyse cells, then perform a centrifugation step. Such a step would remove most cellular components and is considered, by those of skill in the art, as a purification step. The DNA would then meet applicant's second definition of "pure." However, the DNA would not be "unadulterated, free from admixture or contamination with extraneous matter." Moreover, as an example of how the specification provides "pure" antigens, applicant refers to "pure" antigens that can be obtained with various degrees of purity. Clearly, if there are different degrees of purity, these "pure" antigens cannot meet applicant's first definition of a "pure" antigen. If applicant cannot set forth the degree of purity that is necessary, those of skill in the art cannot be expected to "readily understand" what degree of purity is encompassed by the claim. Furthermore, applicant has not addressed how a "pure" antigen that is unadulterated, free from admixture or contamination with extraneous matter, can be in a transdermal vaccine admixed with other matter, and still be considered pure.

As outlined previously, it is unclear what limitations are engendered by the term "pure or purified." Purified and pure are relative terms. To what degree are the antigens to be purified? How are said antigens to be purified? As the claim is drawn using open language (comprising), the composition can contain molecules in addition to the antigen. Is a purified antigen mixed with a contaminant still pure?

The rejection of claim 67 as being rendered vague and indefinite by the phrase "at least one injectable dose of an antigen," is maintained for the reasons set forth in the previous office action.

Applicant argues: that, according to the specification, an "injectable dose" refers to the amount of antigen that would normally be injected into the subject. Applicant asserts that, based on this definition, the term "injectable dose" refers to the dose of the particular antigen injected into the subject.

Applicant's arguments have been fully considered and deemed non-persuasive.

Contrary to applicant's assertion, the specification does not define an "injectable dose." The specification merely states that a preferred embodiment of the invention is a kit that comprises "at least one injectable dose of the antigen described above." This does not limit or describe the "injectable dose" in any way. Since one could inject as much or as little antigen as

one wanted, it is not clear what limitations are engendered by the term "injectable dose." Further, parent claim 66 comprises a dose of the vaccine. Claim 67 further comprises an injectable dose of the vaccine. Does this mean that there are two doses of vaccine, or does applicant intend that the injectable dose be the same dose referred to in the parent? If applicant is referring to the same dose, claim 67 should not say that the kit "further comprises" an injectable dose.

As outlined previously, it is unclear what an "injectable dose" is. Virtually any liquid can be injected. Are there limitations applicant intends by the term "injectable dose"?

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 37, 39-45, 47-48, 50, 55, 58-60, and 62-67 under 35 U.S.C. 103(a) as being unpatentable over Glenn *et al.* (PCT Publication, WO 98/20734, 1998) in view of Paul *et al.* (Vaccine Res., 4:145-164, 1995, IDS filed 12/30/2003), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That Paul does not teach or suggest a vaccine composition comprising an antigen or allergen.

2. That Glenn does not teach or suggest the combination of its transdermal vaccines with the compositions of the claimed invention and Glenn explicitly distinguishes itself from Paul.

3. That there is no motivation to combine the references because both references tech systems that are adequate for the delivery of proteins across barriers.

4. That the references teach away from the instant invention. Applicant asserts that Glenn and Paul state that it is impossible to immunize epicutaneously with simple peptide or protein solutions. Applicant asserts that both references also teach that dermally applied liposomal or mixed micellular immunogens are as inactive as simple protein solutions.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, contrary to applicant's assertion, Paul explicitly suggests a vaccine composition comprising an antigen. Paul teaches a transfersome composition that is the same as applicant's penetrant. Paul states, "we have used bovine serum albumin labelled with fluorescein isothiocyanate (BSA-FITC) to test an astoundlingly new possibility for *in vivo* immunization: vaccination with the full-size proteins across the intact skin" (page 146, paragraph 3). This is clearly a teaching of a vaccine composition comprising an antigen or allergen. The only difference between the elected invention and the composition of Paul is that the composition contains bovine serum albumin rather than tetanus toxoid and IL-12. However, as applicant argues on page 10 or their remarks, "one of skill in the art can practice the invention by merely exchanging one antigen for another."

Regarding argument 2, the examiner recognizes that the Glenn reference distinguishes itself from Paul; however, the rejection was not based solely on Glenn, but rather on the combination of Glenn and Paul. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding argument 3, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where

there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the fact that the composition of Glenn is capable of delivering proteins transdermally does not mean that one would not have been motivated to use the composition of Paul. In addition to the reasons set forth in the previous office action, the following reasons for combining the references are apparent. Glenn does not provide information regarding the efficiency of antigen delivery using their composition, and their composition requires the use of bacterial toxins that are potentially toxic. Whereas the transdermal delivery composition of Paul requires no toxins and has a drug transfer efficiency greater than 90%. In addition, it appears from their arguments that applicant is asserting that the transdermal delivery system of Paul is equivalent to the transdermal delivery system of Glenn. If this is the case, applicant is reminded that it is obvious to substitute equivalents known for the same purpose.

Regarding argument 4, contrary to applicant's assertion, the references do not teach away from the instant invention. Paul explicitly teaches a vaccine composition with the same transdermal delivery penetrant as is instantly claimed. Applicant has miscontrued the statements of Glenn and Paul and has incorrectly reasoned that they teach away from the instant invention. When Glenn and Paul state that it is impossible to immunize epicutaneously with simple peptide or protein solutions, they are saying exactly that. It is impossible to immunize epicutaneously with *simple peptide or protein solutions*. This is in reference to solutions comprising only the peptide or protein, and does not, in any way, refer to the use of transfersomes. In fact, the entire point of both Glenn and Paul is that proteins and peptides *can* be delivered epicutaneously, albeit with the proper transdermal delivery system. Likewise, when Glenn and Paul state that dermally applied liposomal or mixed micellar immunogens are inactive, they are referring to *dermally applied liposomal or mixed micellar immunogens*. These are separate from the transfersomes that Paul has developed.

As outlined previously, the instant claims are drawn to a transdermal vaccine, comprising: (a) a transdermal carrier comprising a penetrant suspended or dispersed in an aqueous solvent, the penetrant in the form of a minute fluid droplet surrounded by a coating of

one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility, the substances forming homoaggregates of one substance and/or heteroaggregates of the at least 2 substances, the average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, being smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains; (b) a compound which specifically has or induces cytokine or anti- cytokine activity; and (c) an antigen or mixture thereof and/or an allergen or mixture thereof. Further limitations to the vaccine include: the vaccine wherein the compound and the antigen or allergen are associated with the penetrant (claim 39); wherein the less soluble substance with the tendency to aggregate is a polar lipid, and the more soluble substance is a surfactant or a surfactant-like molecule (claim 40); wherein the penetrant is between 30 nm and 500 nm (claim 41); wherein the total weight of droplets in the vaccine for use on human or animal skin is 0.01 weight-% to 40 w-% of total mass (claim 42); wherein total antigen concentration is between 0.001 and 40 w-% of the total penetrant mass (claim 43); comprising a low molecular weight chemical irritant (claim 44); wherein the compound is IL-12 (claim 45); wherein the antigen is derived from pathogens triggering tetanus (claims 47-48); wherein the concentration of each compound used is up to 1000 times higher than a concentration optimum established in corresponding tests performed by injecting the vaccine or performing the tests *in vitro* (claim 50); wherein the concentration of the compound from a pathogen is between 10 times lower and up to 1000 times higher than the concentration used with the corresponding injected vaccines employing similar antigen (claim 55); wherein the low molecular weight irritant is a surfactant-like molecule (claim 58); wherein the surfactant-like molecule enhances skin permeation (claim 59); wherein the concentration of the low molecular weight irritant is below by at least a factor of 2 to a factor of 10 or more a concentration which is unacceptable owing to local irritation in tests on the same or a comparable subject (claim 60); wherein the applied dose of the antigen

differs by the factor of 0.1 to 100 from the dose which would have to be used with an injection (claim 62); wherein the applied dose of an antigen is less than 10 times higher than the dose which would have to be used with an injection (claim 63); wherein the applied penetrant dose is between 0.1 mg/cm^2 and 15 mg/cm^2 (claim 64); and wherein the antigen is a pure of purified antigen (claim 65). Further claims are drawn to a kit containing the vaccine of claim 37 in a packaged form (claim 66) and said kit comprising an injectable dose of an antigen (claim 67).

Glenn *et al.* disclose a transdermal vaccine that contains tetanus toxoid and interleukin-12 (see abstract; page 16, lines 15-17; and page 18, lines 15-30). Glenn *et al.* state that the antigens used in the vaccine can be purified (see paragraph bridging pages 15-16).

Glenn *et al.* differs from the instant invention in that the transdermal vaccine does not comprise a carrier wherein the substances forming homoaggregates of one substance and/or heteroaggregates of the at least 2 substances, the average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, being smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains.

Paul *et al.* disclose an transdermal vaccine (see page 146, paragraph 3) that comprises a transdermal carrier known as a transfersome that comprises ethanolic soybean phosphatidylcholine, sodium cholate, and an antigen (see page 148, Transfersomes preparation). Said transfersomes have the same composition as the claimed vaccine carrier and would thus necessarily have the same physical and immunological properties as the claimed vaccine transfersomes. Additionally, Paul *et al.* disclose that transdermal immunization using large protein molecules can be accomplished using said transfersomes, and that, if properly optimized, a transdermal drug transfer efficacy of > 90% can be achieved (see page 162, paragrahs 7-8). Paul *et al.* further disclose that vaccination can be accomplished using full size proteins across the intact skin (see page 146, paragraph 3).

It would have been obvious to one of ordinary skill in the art to use the transdermal carrier (transfersomes) of Paul *et al.* in the vaccine of Glenn *et al.* in order to take advantage of the high drug transfer efficacy of transfersomes, as disclosed by Paul *et al.* One would have had a reasonable expectation of success because Paul *et al.* disclose that their transfersomes are capable of delivering full size proteins across the skin in a vaccination. Regarding claim 40, phosphatidylcholine is a polar lipid and sodium cholate is a surfactant. Regarding claims 44 and 58, the low molecular weight is claimed as a surfactant-like molecule. Sodium cholate is a surfactant, and is thus surfactant-like. Regarding claims 41-43, 50, 55, 60, and 62-64, these claims are merely optimized ranges for materials in the vaccine. Paul *et al.* disclose that the vaccine should be properly optimized to achieve efficacy. Further, according to MPEP 2144.05, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Regarding claims 66 and 67, the vaccine disclosed by the prior art are packaged in some form, thus anticipating the limitation of a kit containing said vaccine in a packaged form. The vaccine taught by the combination of Paul *et al.* and Glenn *et al.* would be injectable. Therefore, as the vaccine disclosed by the prior art contains a dose of antigen, the prior art anticipates this limitation.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

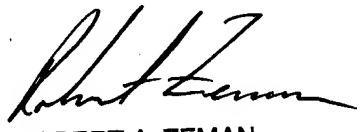
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle
AU 1645



ROBERT A. ZEMAN
PRIMARY EXAMINER